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# The Impact of Endovascular Treatment of Atheroscleroptic Renal Artery Stenosis on Endothelial Function and Arterial Blood Pressure

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# The Impact of Endovascular Treatment of Atherosclerotic Renal Artery Stenosis on Endothelial Function and Arterial Blood Pressure

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# 1. Abstract

**Objectives:** Renovascular disease leads to arterial hypertension and decreases renal function, which both impair endothelial function, a cardiovascular surrogate marker. Two markers of endothelial function, flow-mediated dilatation and reactive hyperemia, are easily and non-invasively assessable by ultrasound. The aim of this study was to investigate the impact of percutaneous transluminal renal artery angioplasty (PTRA) with stenting on endothelial function and arterial blood pressure in patients with renal artery stenosis (RAS).

**Methods:** Flow mediated dilatation of the brachial artery, flow velocities and shear stress were measured with high resolution ultrasound in 24 hypertensive patients with renal artery stenosis (RAS) prior and after revascularization by PTRA with stenting. Endothelial-independent brachial dilatation was measured after application of nitroglycerin.

**Results:** Endothelial-dependent dilatation improved from 2.4 ± 0.9% to 6.1 ± 1.4% ($p=0.03$), whereas endothelial-independent dilatation did not change after PTRA. Endothelial-dependent reactive hyperemic blood flow increased from 195 ± 40ml/min to 536 ± 94ml/min ($p=0.0008$), whereas endothelial-independent hyperemia did not increase after revascularization. After PTRA, shear stress at rest decreased from 37 ± 11 to 23 ± 3 dyne/cm² ($p<0.0001$), and reactive hyperemic shear stress increased from 89 ± 29 to 107 ± 12 dyne/cm² ($p=0.014$). The impact of PTRA on arterial blood pressure resulted in a mean decrease of 21 ± 5mmHg in systolic pressure ($p<0.0001$), of 9 ± 2 mmHg in diastolic pressure ($p=0.03$), and of 14 ± 5mmHg in peripheral pulse pressure ($p=0.00039$), respectively.

**Conclusion:** Endovascular treatment of renovascular disease improves endothelial function and leads to a decrease in resting shear stress. Therefore, endovascular treatment of RAS may have a beneficial effect on cardiovascular risk.

## 2. Introduction

Renovascular disease may cause arterial hypertension through up-regulation of the renin-angiotensin-aldosterone system. In addition, angiotensin II does not only cause vasoconstriction – one factor in renovascular disease for arterial hypertension - but also activates NAD(P)H oxidase, a major source of reactive oxygen species located in smooth muscle cells (1). Reactive oxygen species inactivate endothelial nitric oxide, a potent vasodilator. Therefore, renovascular disease leads to lower nitric oxide (NO) bioavailability and hence an impaired vasodilatatory response.
Catheter-based percutaneous renal intervention has become a widely accepted therapy to treat arterial hypertension and/or renal insufficiency caused by renovascular disease. The effect of percutaneous transluminal renal artery angioplasty (PTRA) on arterial hypertension in patients with atherosclerotic renovascular disease is currently under debate (2-4). An important human in-vivo study elucidated the pathophysiology of oxidative stress and vascular function in renovascular disease (5). Higashi et al. demonstrated that oxidative stress decreases and endothelial dependent dilatation improves following successful PTRA. However, they used invasive vascular testing with brachial artery puncture for the application of vasoactive drugs and subsequent plethysmographic flow assessment to measure endothelial dependent dilatation (5).
In recent years, non-invasive assessment of the endothelial function known as flow-mediated dilatation (FMD) and reactive hyperemia, assessed by high resolution duplex ultrasound at the brachial artery, has become widely accepted and shown to be correlated with systemic NO bioavailability (1). In addition, decreased FMD has been shown to be seen in early phases of atherosclerosis which is helpful in establishing the diagnosis and prognosis of coronary heart disease (6,7,8,9). It is

also associated with an increased risk for cardiovascular events in patients undergoing peripheral arterial surgery (10).

The goal of this study was to investigate the effect of PTRA in patients with renal artery stenosis (RAS) on flow-mediated dilatation and reactive hyperemia, assessed non-invasively by high-resolution ultrasound and on arterial blood pressure.

## 3. Methods

### *Patients*

Patients with arterial hypertension and/or renal insufficiency and unilateral or bilateral RAS (>70%) on duplex scan and angiography were eligible. Exclusion criteria were: recent peripheral arterial or coronary interventions or surgery within the last three months, chronic inflammatory diseases and liver disease. Twenty-four patients (15 men, mean age 70 years, range 50-84) were included. The local ethical committee had approved the study (EK-1293) and all patients had given written informed consent.

### *Study Design*

The study was conducted at a tertiary referral centre as a prospective, open, non-randomised, single-arm, follow-up evaluation, assessing the efficacy of PTRA in patients with RAS on FMD, vasodilatatory capacity and peripheral blood pressure (systolic, diastolic, mean and pulse pressure).

### *Endothelial Dependent Flow-mediated Dilatation and Hyperemic Flow Reserve*

Parameters (brachial artery flow-mediated and nitrate-mediated dilatation, hyperemic flow reserve, mean arterial and peripheral pulse pressure) were assessed one day prior to and one day after PTRA. Measurements were taken after an overnight period of rest. Patients were asked to refrain from smoking, as well as from consuming caffeine and taking antihypertensive drugs for at least 24 hours. Hydration 12 hours prior to the assessment of brachial diameter was standardized with intravenous sodium chloride infusion of 1000ml/12 hours and 500ml/12 hours fluids orally.

Duplex ultrasound assessment of endothelial-dependent FMD of the brachial artery was determined in accordance with recently issued guidelines (11). The study was performed between 8 a.m. to 10 a.m. in a temperature-controlled room (20-22℃) with subjects resting in the supine position prior to and after the intervention. Brachial artery diameter was measured two to five cm above the cubital fossa using a high-resolution (15-MHz line array) transducer ultrasound system (Sequoia, Siemens, Erlangen, Germany) equipped with electronic callipers, vascular software for two-dimensional imaging, colour and spectral Doppler, and internal electrocardiogram. A sphygmomanometric cuff was placed on the forearm. Baseline diameter and Doppler flow signals were recorded. The cuff was inflated at least 50mmHg above the systolic pressure to occlude arterial flow for 5 minutes. Immediately after cuff release Doppler flow signals were recorded during 15 seconds. Measurements were made at the end of the diastole between 30 to 90 seconds after cuff release. After a rest of 10 minutes, to allow return of the brachial artery diameter and flow to baseline state, 2-dimensional brachial images were recorded for a period of 2 minutes and repeated 4 minutes after sublingual application of 0.4mg nitroglycerin.

Blood flow at baseline and during hyperemia was calculated from mean velocity and vessel diameter. FMD was expressed as percentage change from the baseline. Brachial artery shear stress was calculated as 8 x blood viscosity ($\mu$) x brachial artery flow velocity (V) / diameter of the brachial artery. Blood viscosity was assumed to be 0.035 dyne-sec/cm$^2$. Off-line measurements were performed on a personal computer using the analysis software Brachial Reactivity Analysis (Siemens, Erlangen, Germany). The response of the vessel diameter to reactive hyperemia was calculated and expressed as a percent change relative to the diameter immediately before cuff inflation.

***Systolic, Diastolic, Mean Blood Pressure and Peripheral Pulse Pressure***

Systolic and diastolic blood pressures were measured using the Riva Rocci method. Mean arterial blood pressure is expressed as diastolic blood pressure + 1/3 x (systolic pressure – diastolic pressure) and the peripheral pulse pressure as the systolic minus the diastolic pressure. The peripheral pulse pressure is considered to be a superior predictor for cardiovascular mortality compared to the systolic or diastolic values alone (12). Blood pressures were assessed in recumbent position after a rest of 10 minutes 24 hours pre- and postinterventionally between 8 a.m. and 10 a.m.

***Non-invasive Renovascular Assessment***

Only patients with unilateral or bilateral stenosis of >70% were included. The following duplex criteria for relevant stenosis had been used: Reno-aortic peak systolic velocity ratio >3.5, and/or renal artery peak systolic velocity >1.8m/s, differences in resistance index of >0.05 (unilateral stenosis). Follow-up duplex scans were done in all subjects at least one day after the intervention and prior to the assessment of endothelial reactivity and hyperemic response, to rule out acute recoil or residual stenosis of the treated artery. Hemodynamic criteria for successful revascularization included reno-aortic peak systolic velocity ratio <1.5, renal artery peak systolic velocity <1.2m/s and absent differences in resistance indices (<0.05).

***Percutaneous Transluminal Renal Angioplasty with Stenting***

Percutaneous renal intervention was performed using a 6-F arterial introducer inserted in the femoral artery. Patients with renal artery stenosis were included when systolic and mean aorto-renal pressure gradient were greater than 30mmHg and 15mmHg, respectively. Peak and mean renal artery pressure and after drawback of

the guiding catheter aortic pressures were recorded. Subsequently stent implantation was performed in all patients. In the case of tight stenosis the option of predilatation was left to the discretion of the interventionalist. Balloon expandable stents were implanted and postdilatation performed as needed. Final angiogram and pressure measurement (systolic pressure gradient <10mmHg, mean pressure gradient <10mmHg) were performed to confirm technical success. Post-interventional therapy consisted of acetylsalicylic acid 100mg/d and clopidogrel 75mg/d for 4 weeks.

***Statistics***

Data are expressed as mean ± standard deviation (SD). Data were analyzed using Wilcoxon signed rank test for intra-group comparisons. Statview 5.0.1 was used as statistical software. A p-value <0.05 was considered to be significant.

# 4. Results

### *Patients Characteristics*

Characteristics of patients with atherosclerotic RAS at baseline are shown in Table 1.

**Table 1. Baseline Characteristics of the 24 Patients with Atherosclerotic Renovascular Disease**

| | |
|---|---|
| Mean age, years (range) | 70 (50-84) |
| Females, % (n) | 37.5 (9) |
| Body-Mass Index, kg/m² ( ± SD) | 27.2 (± 4.7) |
| Cardiovascular risk factors, % (n) | |
| Hypertension | 100 (24) |
| Diabetes mellitus | 25 (6) |
| Dyslipidemia | 75 (18) |
| Smoking | 46 (11) |
| Cardiovascular Comorbidities, % (n) | |
| Coronary artery disease | 46 (11) |
| Cerebrovascular disease | 13 (3) |
| Peripheral arterial disease | 38 (9) |
| Bilateral renal artery stenosis, % (n) | 28 (7) |
| Cardiovascular Medication, % (n) | |
| Beta-blocker | 50 (12) |
| ACE-Inhibitor | 58 (14) |
| Angiotensin receptor blocker | 25 (6) |
| Calcium channel blocker | 58 (14) |
| Diuretics | 63 (15) |

### *Effects of PTRA on Brachial Artery Diameter and Flow Characteristics*

There was no significant difference between baseline and follow-up measurements of brachial artery diameter at rest. Although brachial artery diameter tended to be larger after PTRA during hyperemia and after sublingual nitroglycerin application, these differences were not significant (Table 2).

When FMD was calculated as percentage increase from resting to hyperemic brachial diameter, there was a significant increase between baseline (2.4 ± 0.9%) and postinterventional FMD (6.1 ± 1.4%, p=0.03), respectively (Figure 1a), whereas endothelial independent FMD did not change (10 ± 1.7 % to 14 ± 2.7 %, p=0.28).

### *Shear Stress and Flow Volume before and after Percutaneous Renal Intervention*

Resting flow volume and shear stress decreased significantly after PTRA (Table 2), whereas mean velocity did not change.

Similarly, the vasodilatation with nitroglycerin produced a lower flow volume and shear stress after PTRA compared to measurements before PTRA (p=0.01 and p<0.0001, respectively), whereas mean velocity tended to be lower (p=0.06). In contrast, hyperemia produced a significantly higher flow volume, higher mean velocity and higher shear stress after PTRA. In addition, when changes of hyperemic flow reserve were calculated as percentage increase to resting values, endothelial dependent hyperemic flow reserve increased by more than twofold from 195 ± 40% to 536 ± 94% (p=0.0008), whereas endothelial independent hyperemic flow reserve did not change significantly (35 ± 17% to 46 ± 24 %, p=0.85, Figure 2a and b).

**Table 2. Brachial Ultrasound Results in Patients with Renovascular Disease at Baseline and after Percutaneous Renal Intervention**

| | Baseline | after PTRA | p |
|---|---|---|---|
| *Resting* | | | |
| Brachial artery diameter, mm (SD) | 3.95 (0.14) | 3.90 (0.16) | n.s. |
| Flow volume, mL/min (SD) | 54 (7.9) | 37 (5.1) | 0.03 |
| Mean velocity, cm/sec (SD) | 46(10) | 29 ( 3) | n.s. |
| Shear stress, dyne/cm² (SD) | 37 (11) | 23 (3) | <0.0001 |
| *Hyperemic* | | | |
| Brachial artery diameter, mm | 4.05 (0.1) | 4.13 (0.2) | n.s. |
| Flow volume, mL/min | 124 (17) | 166 (20) | 0.0087 |
| Mean velocity, cm/sec | 111 (20) | 139 (14) | 0.017 |
| Shear stress, dyne/cm² | 89 (29) | 107 (12) | 0.014 |
| *Nitroglycerin** | | | |
| Brachial artery diameter, mm | 4.38 (0.16) | 4.44 (0.18) | n.s. |
| Flow volume, mL/min | 72 (16) | 43 (7) | 0.01 |
| Mean velocity, cm/sec | 51 (16) | 26 (4) | n.s. |
| Shear stress, dyne/cm² | 38 (15) | 18 (3) | <0.0001 |

All values are mean and standard deviation (SD)

*n=21 for nitrogylcerin-mediated dilatation. Three patients had a contraindication or declined to take nitrogylcerin.

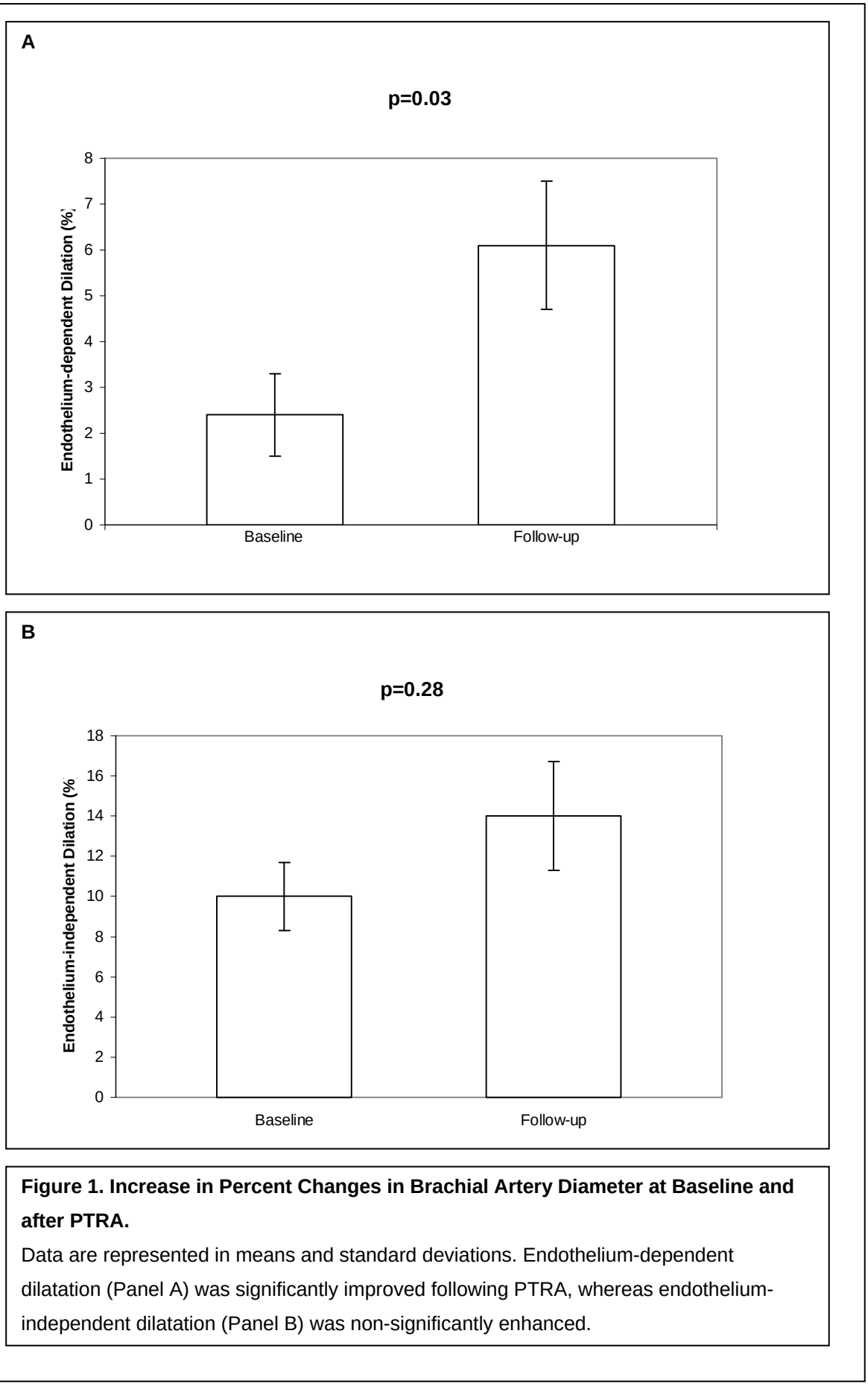


**Figure 1. Increase in Percent Changes in Brachial Artery Diameter at Baseline and after PTRA.**

Data are represented in means and standard deviations. Endothelium-dependent dilatation (Panel A) was significantly improved following PTRA, whereas endothelium-independent dilatation (Panel B) was non-significantly enhanced.

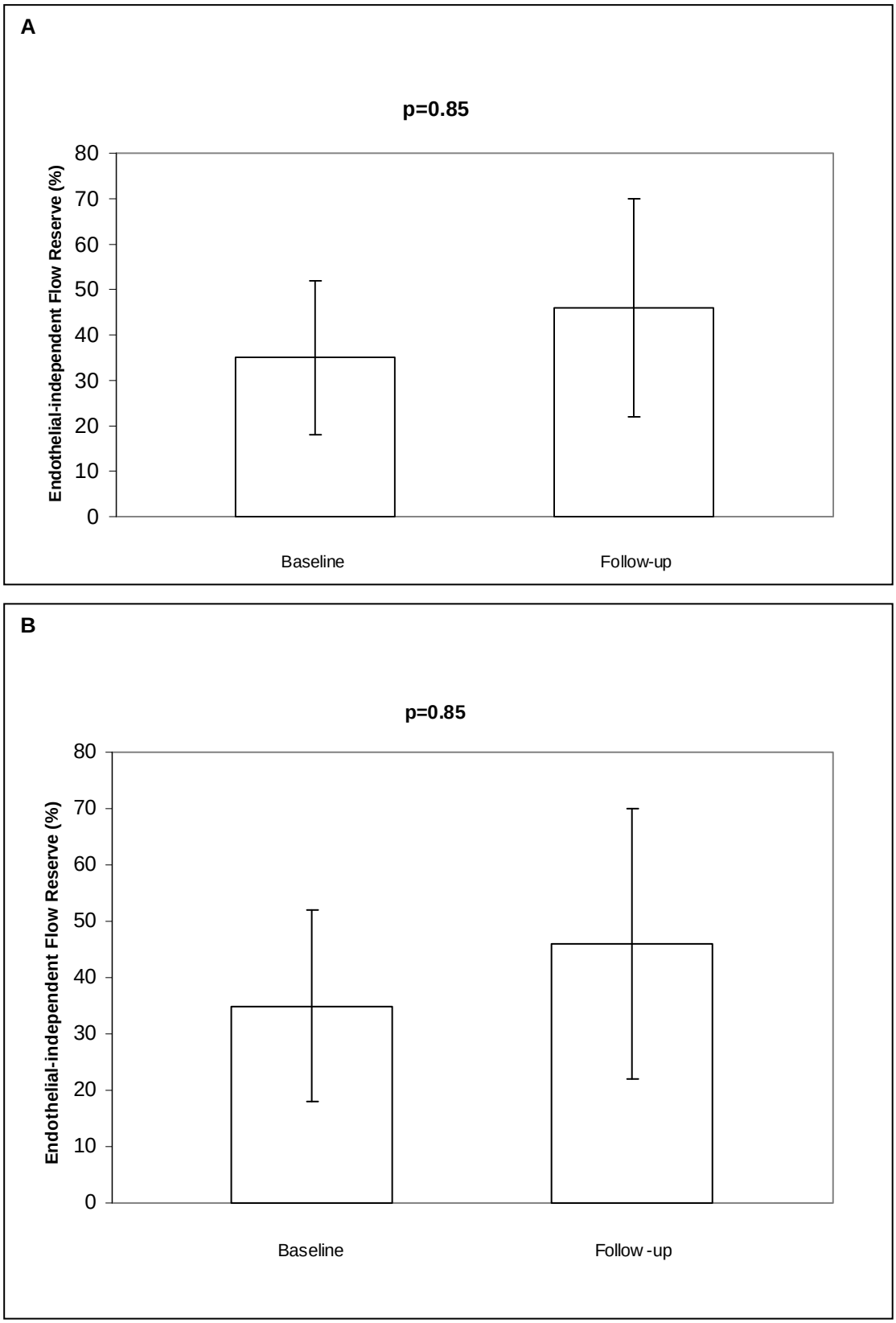


**Figure 2. Increase in Percent Changes in Brachial Arterial Flow Reserve.**
Data are represented in means and standard deviations. Endothelium-dependent (hyperemic) flow reserve significantly rose after PTRA (Panel A), and endothelium-independent (nitrogylcerin-mediated) flow reserve did not significantly improve.

***Systolic and Diastolic Arterial Blood Pressure and Peripheral Pulse Pressure before and after Percutaneous Renal Intervention***

Systolic and diastolic arterial blood pressure were significantly reduced by 21 ± 5mmHg ($p<0.0001$) and 6 ± 2mmHg ($p<0.03$), respectively. Mean arterial blood pressure dropped by 14 ± 4mmHg and the peripheral pulse pressure by 12 ± 5mmHg ($p=0.0003$).

**Table 3. Effects of Percutaneous Renal Intervention on Systolic and Diastolic Blood Pressure, Mean Arterial Pressure and Peripheral Pulse Pressure**

| | Baseline | Follow-up | p |
|---|---|---|---|
| Systolic blood pressure, mmHg | 164 (5) | 143 (5) | <0.0001 |
| Diastolic blood pressure, mmHg | 88 (3) | 79 (2) | 0.03 |
| Mean arterial blood pressure, mmHg | 125 (4) | 111 (3) | 0.0002 |
| Peripheral pulse pressure, mmHg | 78 (5) | 64 (5) | 0.0003 |

All values are mean and standard deviation (SD).

## 5. Discussion

Renovascular disease increases angiotensin II causing peripheral vasoconstriction as well as deterioration of endothelial function through oxidative stress (5,13). This results in impairment of vascular compliance in terms of arterial stiffness and endothelial dependent vasodilatation, both known to be associated with poorer cardiovascular prognosis (14-17).

We assessed endothelial function utilising a non-invasive method through high-resolution ultrasound, to evaluate the association of PTRA on endothelium-dependent and -independent brachial artery changes. FMD was introduced in 1992 by Celermajer *et al.*, and has since been used by numerous groups to monitor endothelial function (11,18). An increase in shear stress, e.g. post-ischemic, results in an increase tangential force exerted by blood flow over the surface of the endothelium. This leads to a rapid activation of endothelial nitric oxide synthase, and consecutive nitric oxide formation, which results in dilatation of the vessel, usually the brachial artery (19-22). Since this method provides a valuable status of local vascular nitric oxide availability, the improvement of FMD in our study can be directly related to a better nitric oxide status (1). Based on previously reported data, PTRA lowers angiotensin II and thereby improves nitric oxide bioavailability (5). The present findings of improved endothelial-dependent dilatation and hyperemic blood flow reflect those of Higashi et. al (5). After PTRA, brachial artery diameter at rest did not differ from preinterventional values, but mean velocity was lower at rest following PTRA, resulting in a lower resting shear stress. In contrast, hyperemic flow was increased after PTRA, representing lower peripheral microvascular resistance and inducing a significantly higher shear stress and endothelium dependent vasodilatation. This increase after PTRA indicates an improved vascular reserve.

Reactive hyperemia is a fundamental response of the vasculature to facilitate rapid oxygen delivery to tissues after a period of ischemia. Hyperemic blood flow peaks within a few seconds after restoration of flow, but declines rapidly thereafter resulting in the aforementioned endothelial dependent dilatation, which occurs 30 to 90 seconds after cuff release. The reactive hyperemia depends on numerous factors such as adenosine, prostaglandins, potassium, pH, hydrogen peroxide and endothelium derived nitric oxide. Several studies have investigated the impairment of reactive hyperemia in relation to cardiovascular events and proposed that this impairment is related to increased cardiovascular risk (6,7,10). This has been assessed in patients with coronary and peripheral arterial disease. Both, reduced FMD and hyperemic flow velocities were shown to be associated with increased risk for future cardiovascular events (6,10). Whether this is true or not for patients with renovascular disease remains to be determined in prospective studies. However, previous studies have shown that the presence of RAS in patients undergoing coronary angiography is a strong independent predictor of mortality (23).

Vascular flow propagation is the combination of steady flow (mean arterial blood pressure) and pulsatile (pulse pressure) components. Although peripheral pulse pressure at the level of the brachial artery does not adequately portray the pulsatile load to the heart like the central pulse pressure, there is recent evidence that increased central pulse pressure is closely related with an increase of peripheral pulse pressure (24). Therefore, the reduction in peripheral pulse pressure and mean arterial pressure, as demonstrated, could indicate an improved vascular compliance. Furthermore, as there is widespread agreement that elevated pulsatile load is associated with increased risk of cardiovascular disease, these reductions in pressure parameters might not only in part be related to the brachial artery hemodynamic, but indicate that the micro- and macrovascular changes following

PTRA could result in lower cardiovascular risk. Zeller *et al.* demonstrated that PTRA induces regression of left ventricular mass that is independent of the reduction in blood pressure. Therefore, further evaluation using the peripheral pulse pressure as well as the assessment of flow-mediated dilatation could contribute to better understanding of these favourable physiological changes due to PTRA (25).

As this is a non-randomized observational study of a subgroup of individuals with renovascular disease, our findings cannot be gerenalized to all patients with renovascular disease. In addition, the effect of PTRA on vascular function might also be achieved by optimal use of antihypertensive medication. In contrast the ASTRAL trial report that PTRA is not superior to conservative medical treatment alone in patients with renal artery stenosis regarding cardiovascular and renal endpoints. Future randomized studies are needed to compare the effects of best medical treatment and PTRA on vascular function.

In conclusion, PTRA resulted in an improved endothelial function and reduction of peripheral pulse pressure suggesting amelioration of systemic vascular compliance. This might have implications for cardiovascular prognosis in patients with renal artery disease.

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